Review Article

Paroxysmal Hemicrania

Chinar Osman, Anish Bahra[1]

Wessex Neurological Centre, Southhampton General Hospital, Southhampton, England, [1]Headache Service, National Hospital for Neurology and Neurosurgery, London, UK

Abstract

Paroxysmal hemicrania (PH) is a primary headache disorder belonging to the group of trigeminal autonomic cephalalgias(TACs). Patients typically experience intense lateralzsed headaches with pain primarily in the ophthalmic trigeminal distribution (V1) associated with superimposed ipsilateral cranial autonomic features. PH is distinguished from other TACs by an exquisite responsiveness to therapeutic doses of indomethacin. Patients may need to be maintained on indomethacin for several months before trials of reduction can be attempted. The disorder does have a tendency toward chronicity. PH is uncommon, but early recognition will prompt initiation of effective treatment to avoid unsuccessful trials of drugs effective in other primary headaches. As with other TACs, hypothalamic and trigeminovascular mechanisms are implicated in the pathophysiologic mechanism of PH. Neuroimaging findings in PH demonstrate a posterior hypothalamic activation similar to that observed in the other TACs. This review will address the epidemiology, clinical presentation, pathophysiology, evaluation, and treatment of PH.

Keywords: Indomethacin, paroxysmal hemicrania, trigeminal autonomic cephalalgias,

Introduction

Paroxysmal hemicrania (PH) was first reported in two patients by Ottar Sjaastad and Inge Dale in 1974.[1] Two years later, they named this disorder chronic paroxysmal hemicrania (CPH). The first patient described had daily headaches for 9 years that had been refractory to treatment. Sjaastad wrote, "In the course of testing corticosteroids and nonsteroidal anti-inflammatory agents, indomethacin proved to have a miraculous effect."

CPH was introduced to the International Headache Society (IHS) classification system in 1988. Over subsequent years, it was recognized that some patients experienced a chronic pattern of symptoms while others had recurrent bouts, interspersed by more prolonged pain-free remission periods. This led to the subdivision of PH into episodic and chronic forms in the 2004 IHS criteria.

The diagnosis is clinically supported by a complete and dramatic response to an adequate trial of indomethacin.

Epidemiology

PH has been described in several countries including within Europe, Canada, the United States, Mexico, Brazil, India, and New Zealand.[2,3] Despite this, there is a lack of epidemiological studies addressing the prevalence of PH. The Vaga study found one possible case of PH from 1838 parishioners aged 18–65 years questioned face-to-face in search of rare unilateral headaches.[4] In a recent prospective study, Ramon reviewed 100 unilateral side-locked headaches in a specialist adult headache clinic and found that hemicrania continua affected 8% of patients and PH was diagnosed in 4% of patients. In comparison, cluster headache accounted for 38% of the cohort.[5]

Sex Distribution

A case series of 84 patients in 1989 found a female to male sex ratio of 2.36:1.[6] A more recent prospective study of 31 patients found a female to male ratio of 1:1[7] similar to a smaller retrospective cohort of 22 patients.[8] This is in contrast to cluster headache which is about three times as common in men.[9,10]

Family History

PH has been reported in one family.[11] Genetic studies on PH are hampered by small sample size.

Address for correspondence: Dr. Anish Bahra, National Hospital for Neurology and Neurosurgery, Box 80, Queen Square, London WC1N 3BG, UK.
E-mail: anish.bahra@bartshealth.nhs.uk

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History of other Primary Headache Disorders

In Cittadini's prospective study, 51% (16/31) had a personal history of migraine and 58% of patients (18/31) had a family history of migraine or a headache not otherwise specified or both.[7] Taking into account sex ratios, as observed in cluster headache (26%),[9] hemicrania continua (61%)[12] and short-lasting unilateral neuralgiform headache attacks (SUNA) (40%),[13] the prevalence of migraine is higher in the TACs than compared to the population-based figure of 12%.[14]

Patients have been described with bouts of both trigeminal neuralgia and PH. This has led to the term chronic PH-tic syndrome.[15,16] Each syndrome responded to the individual therapy associated with successful treatment of that disorder. PH has been reported to co-occur with primary cough and stabbing headache, which are also indomethacin-sensitive.[17]

Age of Onset

The mean age of onset is usually between the fourth and fifth decade although cases with childhood onset and as old as 81 years have been documented.[6,7,18,19]

Pathophysiology

The pathophysiology of PH is reflected in the diagnostic terminology of the trigeminal autonomic cephalalgias, which is both descriptive but also serves to emphasize the prominent activation of both the trigeminal and autonomic pathways. Delineation of the components of the pathophysiological pathway has been gained through clinical observations, genetic studies in headache, biochemical, electrophysiological, and functional imaging studies.

Genetic studies

It is becoming clearer that individuals who experience primary headaches have a genetic predisposition. There are now numerous mutations in three causative genes in hemiplegic migraine: the CACNA1A, K/Na-ATPase, SCN1A genes[20] and the recently reported role of TRESK in migraine with typical aura.[21] Functional consequences of such mutations have been shown to cause alteration in neuronal excitability. Moreover, alternating phases between loss and gain of function would explain the periodic nature of these disorders.[22,23] Cluster headache is 13–14 times more likely to be found in a first-degree relative of a sufferer, compared to the population.[24,25] There are reports of cluster headache across three generations, suggesting an autosomal dominant pattern in some families.[26] There are also reports in monozygotic and dizygotic twins.[27] The reports of familial cases in the less prevalent PH,[11] SUNA[28] and hemicrania continua[29] also support genetic susceptibility of the TACs.

Electrophysiology

Pain and pressure threshold, nociceptive flexion reflex, and blink and corneal reflexes have been studied in a cohort of 12 patients with CPH. The corneal reflex threshold was found to be reduced bilaterally during CPH attacks reflecting the activation of the trigeminal pathways.[30] Drummond reported greater heat loss from the region of the orbit, nose, cheek and temple on the symptomatic side during headache by 0.75ºC–1.5ºC and 0.25ºC–0.75ºC greater between headache episodes.[31] Horven showed an increase in ocular blood flow in PH during attacks compared to the interictal period.[32] Both studies suggest parasympathetic activation during attacks.

Biochemical studies

Goadsby and Edvinsson demonstrated that patients with CPH had elevated levels of calcitonin gene-related peptide (CGRP), a marker of trigeminal nociception, and vasoactive intestinal polypeptide (VIP), a marker of parasympathetic activation (VIP), in the cranial circulation during acute attacks. Furthermore, levels normalized following successful treatment with indomethacin.[33] The efficacy of novel drug therapies targeting CGRP in migraine and cluster headache[34] offers optimism about potential benefit in PH as an alternative to indomethacin, use of which limited by its adverse event profile.

Functional imaging

Functional imaging studies have further strengthened the pathophysiological role of a centrally driven trigeminal autonomic pathway. As in the rest of the TACs,[35,36] there is signature activation of the posterior hypothalamus. This activation was shown to be present during spontaneous attacks and the interictal pain-free state but not in the treated pain-free state after Indomethacin.[37]

Clinical Features

The clinical features of PH are given in Table 1.

The pain is characteristically unilateral but can switch sides between attacks and rarely can be bilateral.[38] Pareja reported a case of a woman who, after treatment withdrawal from indomethacin, developed incomplete attacks on the usually symptomatic side, with autonomic symptoms but without pain.[39]

The character of the pain in PH is usually severe in intensity and has been described by patients as sharp, stabbing, throbbing, shooting, burning, or boring. The pain usually has an abrupt onset and cessation.[6] In Cittadini's study of 31 patients, the pain was reported primarily in the distribution of the ophthalmic division of the trigeminal nerve and C2, followed by the maxillary-mandibular and C3 distributions [Table 2].

In one series, two-thirds of patients had accompanying photophobia and phonophobia, usually lateralizing to the side of the pain.[40] In contrast, photophobia associated with migraine is unilateral in <15% of patients. Although patients with PH may experience nausea, vomiting is rare. Similarly to cluster headache, restlessness and agitation are frequently experienced during attacks. In one retrospective study of PH, half of patients were agitated during the attacks.[6] In Cittadini's

Table 1: Diagnostic criteria for paroxysmal hemicrania[42]

A. At least 20 attacks fulfilling B-E
B. Severe unilateral orbital, supra-orbital, and/or temporal pain lasting 2-30 min
C. Headache is accompanied by at least one of the following signs or symptoms ipsilateral to the pain
Conjunctival injection and/or lacrimation
Nasal congestion and/or rhinorrhea
Eyelid edema
Forehead and facial sweating
Forehead and facial flushing
Ipsilateral miosis and/or ptosis
D. Attacks have a frequency >5 per day for more than half the time
E. Attacks are prevented absolutely by therapeutic doses of indometacin
F. Not better accounted for by another ICHD-3 disorder
Episodic paroxysmal headache
Attacks of paroxysmal hemicrania occurring in periods lasting from seven days to one year, separated by pain-free periods lasting at least one month
Chronic paroxysmal headache
Attacks of paroxysmal hemicrania occurring for more than one year without remission or with remission periods lasting less than one month

ICHD = International classification of headache disorders

Table 2: Distribution of pain in paroxysmal hemicrania[7]

Location of pain	Affected (%)
Temporal	82
Orbital	67
Frontal	64
Retro-orbital	59
Occipital and parietal	54
Vertex and periorbital	51
Neck	33
Maxillary and ear	30
Upper teeth	20
Shoulder	18
Nose	15
Jaw	15
Eyebrow and lower teeth	10
Retro-auricular	8
Upper and lower gum	2

cohort, 80% of patients were restless, agitated or both, while 25% became aggressive.[7]

PH attacks are usually spontaneous and unlike in SUNA cutaneous triggers are uncommon. Approximately 10% of patients experience mechanical triggers such as bending or turning the head.[7] Preceding trauma was observed in 5 of 22 patients.[41] When identified, other triggers have included stress or relaxation after stress, alcohol, exercise, and cold or warm environments.

PH attacks typically last between 2–30 min although attacks lasting up to 4 h have also been described. An interictal background pain, in the same distribution of the typical attacks of PH, can be experienced. The frequency of attacks is reported between 0 and 50 a day. The mean lies between seven and 13 attacks per day.[7,41]

The temporal pattern PH is classified into episodic and chronic forms with the chronic form being four times more common. In chronic PH, patients suffer from attacks over the course of a year either without remission or with a remission period of less than a month. Patients with episodic PH experience attacks at least twice a year lasting from anywhere between 1 week and 1 year with remission periods of least 1 month separating them.[42] There can be two temporal patterns with PH, where the episode stage may be preceded by a chronic stage and vice versa.[6]

In contrast with cluster headache, there is no clear nocturnal preponderance; patients regularly experience both daytime and nocturnal attacks.[41] Nocturnal attacks associated with the rapid eye movement phase of sleep have been described.[43] There is generally no circannual element to the timing of PH headaches although some patients can experience a seasonal preponderance to symptomatic periods.

There is no clear relationship between menstruation or the menopause and PH. The oral contraceptive pill and hormonal replacement therapy do not have any clear effect on symptoms. There is limited data available on the use of indomethacin in pregnancy. It is considered advisable to taper off if patients are trying to conceive although one large cohort study showed no increased risk of spontaneous abortions in patients taking nonsteroidal anti-inflammatory medications during pregnancy.[44] In one case report, a patient with PH stopped indomethacin as she was trying to conceive and became pregnant in her 2nd month of trying to conceive. While, she had persistent headaches in the first trimester, she was then headache free in her second and third trimester.[41]

The "Indotest"

The "indotest," whereby an injection of 50–100 mgs indomethacin is given intramuscularly and compared with placebo, has been used as a diagnostic test for PH. In one study, 6 patients received 50 mg on day one and 100 mg on day two. Two patients also received a placebo. Patients reported complete pain relief for a mean of 8.2 ± 4.2 h (50 mg) and 11.1 ± 3.5 h (100 mg) compared to pretreatment interval of 51 ± 18 min.[45] The placebo arm showed no significant response, mean 94 min pre, and 58 min after treatment. In another study, seven patients reported pain resolution after 13.4 ± 7.7 h. The indotest has the advantage that the diagnosis can be rapidly established but is not widely used in clinical practice. The more widely used regimen is for an oral Indomethacin trial [Table 3].[46]

Differential Diagnosis

The main differential diagnoses of PH are the other TACs.

Hemicrania continua

PH and hemicrania continua, unlike cluster headache and SUNA, exhibit a robust response to Indomethacin. It may be

Table 3: Oral indomethacin regimen[46]

Indomethacin (with concomitant gastroprotection)
Start 25 mg tds for 3 days
Increase to 50 mg tds for 10 days
Increase to 75 mg tds for 10 days
Aim to maintain lowest effective dose and tailor according to activity of the disorder
Six monthly monitoring of renal function advisable

challenging to differentiate between PH and HC particularly in patients with PH and interictal pain. A careful history, in conjunction with a headache diary, can be helpful in discriminating between the two. It is thought that HC usually has less pronounced autonomic features when compared to PH and that the background pain in HC is more severe than the interictal pain experienced by patients with PH.[12]

Cluster headache

The mean attack duration in PH is shorter and the mean attack frequency greater that in patients with cluster headache.[9,47] The characteristics seen in CH of restlessness, alcohol triggering, circannual and circadian rhythmicity of attacks and bouts, are less frequently observed with PH. However, PH and CH can prove difficult to distinguish clinically, especially when CH attacks are of shorter duration or frequency is on the higher side.

Indomethacin is ineffective at treating CH; however, there are anecdotal reports of patients who phenotypically have attacks with duration and frequency typical for cluster headache but who responded to indomethacin.[48-50] Of note is that both patients did not respond to treatments effective for CH.

Short-lasting unilateral neuralgiform headache attacks

PH has a longer attack length and less frequent attacks when compared to SUNA. Patients with SUNA experience attacks lasting between 1–600 s and can have up to 200 attacks per day. Attacks can occur both spontaneously and triggered by both trigeminal and extratrigeminal triggers, such as eating, cold wind, and neck movements.[13] Indomethacin is typically ineffective. In patients presenting with purely spontaneous attacks of longer duration a trial of Indomethacin may be prudent.

Secondary Paroxysmal Hemicrania

The association of a headache disorder with a co-existing pathology is deemed causal, by the Headache Classification Committee of the IHS, if there are a temporal correlation and treatment of the pathology results in resolution of the headache disorder.[42] Yet, one cannot definitively make this assumption on the basis that the improvement may be related to the intervention rather than the pathology, placebo response, or natural history. Moreover, reported cases can respond to indomethacin and be clinically identical to the primary disorder[51] while the reported pathologies vary widely in nature and anatomical site. As with other headache syndromes, the most reliable features indicating a co-occurring disease process is in the history of additional features and the examination.[51,52] This would apply to the apparent reported preponderance of pituitary adenomas associated with TACs, as reported by Levy in a tertiary population.[53] Functioning pituitary tumors were more commonly associated with all headache types particularly growth hormone-secreting adenomas, and prolactinomas. Functioning adenomas were found in one of the three adenomas in cluster headache, all 4 cases of SUNA and the single case of hemicrania continua. A family history of headache was found to be more significantly associated with the incidence of headache in pituitary adenoma patients than size of the lesion, suggesting a genetic predisposition to headache.

The case of a functioning pituitary is relatively straightforward; treatment is of the associated endocrine disorder, and if there is neurological compromise from mass effect, despite medical treatment, surgery is warranted. Yet, this does not guarantee resolution of the headache. Levy reported worsening of headache in three of 10 patients treated surgically. Patients with a functioning adenoma tend to present with the associated systemic symptoms.

The estimated prevalence of incidental pituitary adenoma is 10%. The literature on prognosis of nonfunctioning pituitary adenomas is generally heterogeneous and of low quality. In studies of incidental nonfunctioning pituitary adenoma, macroadenoma are less common and are more likely to increase in size, thus monitoring is advised.[54,55] A lower proportion of nonfunctioning microadenoma progress to increase in size or become functioning adenomas. The recommendation for incidental microadenomas has been made for serial imaging, increasing in duration between imaging over time if there is no change.[56] Yet, it seems that a more pragmatic exercise would be serial visual-field testing and as indicated by symptoms, testing of endocrine function. Surgical intervention has neither guarantee of "cure" of the headache, nor "cure" of tumour, the latter based upon recurrence of surgically treated lesions. Moreover, given that secondary PH can respond equally well to medical treatment as primary PH, it would seem sensible that the two should be managed independently.

Thus, the question remains: should all patients with a TAC be screened for a pituitary lesion driving the disorder? The literature suggests a good history addressing endocrine function and visual fields is more likely to have an impact on management than routine imaging.[57]

Iatrogenic PH has been reported. PH has been reported to have been precipitated by the use of phosphodiesterase inhibitors[58] the attacks were prevented by indomethacin.

Treatments

Acute treatment

Although there are occasional reports of partial acute response to sumatriptan in PH, largely sumatriptan remains ineffective.[7,59,60] In one small open-label study, subcutaneous

sumatriptan 6 mg was tried in 7 patients with CPH and 7 patients with HC without demonstrable efficacy.[61] Oxygen, which is effective in CH, is typically ineffective in PH.[7]

Preventative treatment

Indomethacin

Indomethacin was initially used to treat pain in rheumatological disease and was subsequently introduced as treatment for headache disorders in the 1960s. It was initially used as a treatment for migraine but is no longer recommended in either the European or United States guidelines.

Indomethacin response can be gained with doses ranging from 25 mg to 300 mg.[7,8,41] In one study, 11 patients had been successfully treated with oral Indomethacin. Patients were asked to stop their medication, wait until attacks recurred, and then restart their oral regimen to see how long it took to regain therapeutic response. All patients developed a therapeutic response within 48 h, some as soon as 8 h with cumulative dose range between 25–250 mg.[46] Based upon this, patients can be started on 25 mg tds for 3 days, hence, increased to 50 mg tds for 3 days and if needed higher doses. Some patients may take a week to respond.[8] The mean daily dose requirement from the reported cohorts is 150 mg. Discontinuation or missed doses during active periods usually results in symptom recurrence within a day.

In Cittadini's series of PH, two-thirds of patients developed side effects at some point on indomethacin, which were predominantly gastrointestinal (GI) problems.[7] Boes reported 2 out of 25 patients on indomethacin developed side effects; one patient reported GI disturbance and the other a nonfatal rash.[41] Pareja studied 26 patients with either HC or PH during an average of 3.8 years after onset of treatment with indomethacin. Nearly, a quarter experienced side-effects which were usually GI related and responsive to ranitidine.[62] Thus, it is recommended that Indomethacin is prescribed concomitantly with a proton-pump blocker or H2 antagonist.

Boes retrospective review of 74 patients with CPH showed that of the 75% of patients who showed a clear response to Indomethacin, nine patients were able to stop the Indomethacin after an unspecified amount of time without headache recurrence.[41]

The goal is always to maintain the lowest effective dose throughout. Thus, once symptom control has been achieved for 3–6 months (the actual time-frame is arbitrary) a slow taper can be trialed to achieve the lowest effective dose. Some patients may be able to withdraw completely. If the symptoms recur, the treatment can be reintroduced to manage the associated disability. Indomethacin does not alter natural history.

Other nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors

For patients who are unable to tolerate indomethacin, other NSAIDs such as asprin, naproxen, and diclofenac have been reported to be beneficial.[63] Long-term use of NSAIDs is additionally associated with a risk of renal impairment which may limit their use; it is therefore advisable that patients who are maintained on indomethacin have their renal function monitored every 6 months.[64]

There are reports of efficacy of the Cyclooxygenase-2 (COX-2) inhibitors including celecoxib and rofecoxib.[65-67] The Food and Drug Administration (FDA) has warned that COX-2 inhibitors can increase the risk of myocardial infarction and stroke.[68] They can cause or worsen preexisting hypertension. Rofecoxib was taken off the market in 2004 and celecoxib carries a FDA-mandated "black box warning" for cardiovascular risk.

Other treatments

Calcium channel blockers such as verapamil and flunarizine have shown a therapeutic response in some patients with PH. In 10 patient case series, half of the patients reported a good response to high-dose Verapamil (up to 320 mg/day) in an open trial.[63] Topiramate has shown efficacy in a small number of case reports and in patients refractory to indomethacin and without contraindications.[69,70] The efficacy of a number of other medications including dihydroergotamine, methysergide, acetaminophen with caffeine, lamotrigine, gabapentin, and lithium carbonate have also been reported in case series or case reports.[64] There is a dearth of support for the benefit of local nerve blockade in PH.[71] There is a single case in the literature of a patient with PH who experienced a completed resolution in symptoms following deep brain stimulation of the ipsilateral posterior hypothalamus.[72]

Conclusion

Early diagnosis of patients with PH is crucial to save ineffective interventions. PH is one of the few primary headache disorders that show such an exquisite response to a single medication. Given the small number of subjects reported with this rare primary headache disorder, there is a need to validate the current findings in larger cohorts through national and international collaborative studies. Until, there is more comprehensive data, new onset PH or that associated with additional systemic or neurological features should be imaged. Further work needs to be done in relation to treatment options, particularly on safe and effective treatments for patients who cannot tolerate indomethacin or where it is contraindicated.

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Conflicts of interest

There are no conflicts of interest.

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